REMARKS

Status of the Claims

Claims 14, 16, 18-27, 30-41, and 45-53 are currently pending. Claims 1-13, 15, 17, 28, 29, and 42-44 have been cancelled without prejudice or disclaimer of the subject matter claimed therein. Claims 22-27, 30-41, and 45-53 have been withdrawn as being directed to a nonelected species. Accordingly, claims 14, 16, and 18-21 are currently under examination.

Amendment to the Specification

The specification has been amended to insert the heading "Brief Description of the Drawings" before the paragraphs describing the drawings on page 18, line 22. The amendment to the specification does not introduce prohibited new matter.

Amendment to the Claim

Although claims 35 and 38 have been withdrawn from examination, claim 35 has been amended for clarification of the claimed invention and claim 38 has been amended to provide a definition for R^1, R^2, R^a, R^4, X_1 to X_4, and Y. Support for the amendment to claim 38 can be found in claim 35 from which claim 38 originally depends. The amendment to claim 38 does not introduce prohibited new matter.

Objection to the Specification

The specification has been objected to for missing a heading for the brief description of the drawings. The specification has been amended on page 18, line 22 to include such a heading.

Objection to the Claim

Claim 18 has been objected to for reciting "Cgl", "Aze", "Pab". Applicants assume that claim 19 instead of claim 18 is objected to, since claim 18 does not contain these annotations.

Applicants respectfully point out that "Cgl", "Aze", and "Pab" are defined on page 5, lines 9-11 of the specification. When claim 19 is read in light of the specification, it is clear as to what the annotations refer.

Rejections Under 35 U.S.C. § 102(b)

Claims 14, 16, and 18-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Gustafsson (WO 02/36157).

The Office Action alleges that Gustafsson anticipates the claimed invention because Gustafson teaches administration of melagatran for the treatment of ischemic disorders in patients having or at risk of atrial fibrillation and because Applicants have not provided an explicit definition for the patient population receiving the claimed treatment.

Applicants respectfully point out that the claims as they stand are directed to a method of lowering cholesterol comprising administering melagatran or a pharmaceutically acceptable derivative thereof to a patient in need of such therapy.

In contrast, Gustafsson relates to the use of melagatran and its derivatives in the treatment of ischemic disorder in a patient having or at risk of atrial fibrillation (AF), such as non-valvular atrial fibrillation (NVAF). On page 1, paragraphs 2 and 3, Gustafsson describes AF as "grossly disorganized atrial electrical activity that is irregular in respect of both rate and rhythm" and characterizes patients with AF as having "no visually discernible timing pattern in atrial electrical activity when measured by surface ECG, or in electrogram sequences recorded by catheter electrodes." Moreover, such patients may experience "irregular heartbeat, palpitations, discomfort, dizziness and/or angina pectoris." Gustafsson also states that "current drug therapies for AF include antiarrhythmic drugs, administered with a view to re-establishing a normal heartbeat, and anticoagulant and/or thombolytic drugs, administered with a view to preventing thromboembolism and/or cerebral stroke" (page 2, lines 11-14). Gustafsson does not teach the use of melagatran to lower cholesterol in a patient. Moreover, the patient population of Gustafsson is defined as those having or at risk of AF.

The present specification describes the patient population as those that would benefit from the claimed treatment of lowering cholesterol. As an example, the specification on page 6, lines 7 to 23 states that a "cholesterol-lowering therapy includes any therapy that results in beneficial modifications of serum profiles of total cholesterol, lipids (including triglycerides), lipoproteins, or apolipoproteins . . . ." Accordingly, the claimed method is directed to treating patients that would benefit from reduced cholesterol levels, which is different from the method disclosed by Gustafsson, directed to treating patients having or at risk of AF.

A patient requiring cholesterol-lowering therapy is different from a patient requiring treatment of ischemic disorder because these two groups of patients are associated with different symptoms and therefore are treated different. A patient having AF may not have high cholesterol level, while a patient having high cholesterol level may not have AF. Thus, there is no discernible link between these two groups of patients and one would not expect to treat these two types of disorders using the same method.

The differences between patients having AF and patients having high cholesterol levels can be found in a standard drug reference textbook, such as the *The Complete Drug Reference,* 34th Edition, Martindale, pages 809 to 841 (see attached pages 810 to 814 and 823 to 825). As an example, column 1, page 813 of *The complete Drug Reference,* describes "Angina pectoris," which is associated with AF, "as a syndrome that arises from an inadequate myocardial oxygen supply (myocardial ischemia) and is part of the spectrum of coronary or ischemic heart disease," and explains that ischemia occurs when blood flow either cannot be increased or is reduced. As discussed on page 813 column 2, treatment of angina pectoris includes the use of anticoagulants. Page 810 of *The Complete Drug Reference* provides examples of anticoagulants such as low molecular weight heparins, which are direct anticoagulants, and warfarin, which are indirect anticoagulants. Accordingly, current drug therapies for treating ischemic disorders in patients having AF include anticoagulants, which is also taught by Gustafsson.

Cholesterol-based diseases, on the other hand, are different from AF. As shown on column 2 on pages 823 to column 1 on page 825 of *The Complete Drug Reference*, hyperlipidemias, which is associated with high cholesterol levels, are treated with lipid regulating drugs such as statins, bile-acid binding resins, nicotinates and omega-3 triglycerides (columns 2 and 3 on page 811).

Clearly, the lipid regulating drugs used to lower cholesterols and the anticoagulants used to treat AF are structurally and functionally distinct drugs. Thus, AF and cholesterol-based diseases are completely separate disorders requiring different drugs to treat different patients. Moreover, the cited reference, Gustafsson relates to the use of melagatran and derivatives thereof as a direct thrombin inhibitor to improve anticoagulant treatment for patients with an ischemic disorder. Gustafsson does not teach the use of melagatran to lower cholesterol in a patient in need thereof. Moreover, neither Gustafsson nor *The Complete Drug Reference* teaches that

anticoagulants are effective in lowering cholesterol in a patient.

Accordingly, given that Gustafsson teaches the use of melagatran to treat AF, Gustafsson does not anticipate the claimed invention.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicant respectfully requests entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should an interview be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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The Complete Drug Reference 34th Ed Martindale

on the repolarisation phase, and markedly prolong the PR and QRS intervals.

Described in this chapter are

Encainide, p.910	Pilsicainide, p.983
Flecainide, p.916	Propafenone, p.988
Lorcainide, p.947	

Class II drugs are characterised by beta-blocking activity, leading to a reduction in heart rate, myocardial contractility, and the rate of conduction of impulses through the conducting system.

Described in this chapter are

Beta blockers (but sotalol has predominantly class III activity), p.868	Bretylium, p.876

Class III drugs prolong the repolarisation phase of the action potential.

Described in this chapter are

Acecainide, p.848	Dofetilide, p.906
Amiodarone, p.859	Ibutilide, p.938
Azimilide, p.866	Nifekalant, p.972
Bretylium, p.876	Sotalol, p.1001
Cibenzoline, p.883	

Class IV drugs block the slow inward calcium current (calcium-channel blockers) although not all drugs that fall into the broad general category of calcium-channel blockers share the same specific properties.

Described in this chapter are

Cibenzoline, p.883	Verapamil, p.1019

Many antiarrhythmics have actions typical of more than one class of compound making allocation to one specific class difficult. In some cases this results in multiple classification; an example is bretylium which has class II and III actions. However, in other cases a compound has been allocated to only one class even though it does display additional properties typical of another class; thus propafenone is usually recognised as a class Ic drug although it does possess some beta-blocking activity; beta blockers such as propranolol are traditionally described as class II drugs despite possessing some class I actions; sotalol has some class II actions typical of the beta blockers generally, but has predominantly class III activity and is usually described as a class III drug. Some drugs such as adenosine and digoxin do not fit into the Vaughan Williams classification at all.

The Vaughan Williams classification has been criticised because the electrophysiological action of the antiarrhythmic drugs is not clearly related to their effectiveness in treating a particular arrhythmia in an individual patient. A more clinically useful method might be to categorise the drugs according to the cardiac tissues which each affects. Thus drugs that act on the sino-atrial node include beta blockers, class IV antiarrhythmics, and cardiac glycosides such as digoxin; class I and class III antiarrhythmics act on the ventricles; and drugs acting on atrial arrhythmias include class Ia, Ic, and III antiarrhythmics and beta blockers. Class Ia and III antiarrhythmics act on accessory pathways and drugs acting on the atrioventricular node include class Ic and IV antiarrhythmics, beta blockers, and cardiac glycosides. A simplification of this scheme is to classify drugs into those that act on both ventricular and supraventricular arrhythmias such as amiodarone, beta blockers, disopyramide, procainamide, and quinidine, those that act mainly on ventricular arrhythmias such as lidocaine, mexiletine, and phenytoin, and those that act mainly on supraventricular arrhythmias such as verapamil.

References.

1. Vaughan Williams EM. Classification of antidysrhythmic drugs. *Pharmacol Ther* 1975; 1: 115–38.
2. Harrison DC. Current classification of antiarrhythmic drugs as a guide to their rational clinical use. *Drugs* 1986; 31: 93–5.
3. Frumin H, *et al.* Classification of antiarrhythmic drugs. *J Clin Pharmacol* 1989; 29: 387–94.
4. Nattel S. Antiarrhythmic drug classifications: a critical appraisal of their history, present status, and clinical relevance. *Drugs* 1991; 41: 672–701.
5. Vaughan Williams EM. Classifying antiarrhythmic actions: by facts or speculation. *J Clin Pharmacol* 1992; 32: 964–77.

Anticoagulants

Anticoagulants are used in the treatment and prophylaxis of thromboembolic disorders. They may be divided into direct anticoagulants such as the heparins, low-molecular-weight heparins, heparinoids, and direct thrombin inhibitors, and indirect anticoagulants such as the coumarin and indanedione derivatives.

Direct anticoagulants

Heparin inhibits clotting of blood *in vitro* and *in vivo* by enhancing the action of antithrombin III. Antithrombin III, which is present in plasma, inhibits the activity of activated clotting factors including thrombin (factor IIa) and activated factor X (factor Xa). With normal therapeutic doses heparin has an inhibitory effect on both thrombin and factor Xa. The low doses that are given subcutaneously for the prophylaxis of thromboembolism have a selective effect on antithrombin III's inhibition of factor Xa. Very high doses are reported to reduce the activity of antithrombin III. Heparin also has some effect on platelet function, inhibits the formation of a stable fibrin clot, and has an antilipidaemic effect.

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Like heparin, these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin activity) than heparin. Although the possibility that such selective factor-Xa inhibition would result in antithrombotic activity without anticoagulant, and hence haemorrhagic, effects has not been confirmed by clinical experience, they have more predictable effects and require less monitoring than heparin. Low-molecular-weight heparins also have less effect on platelet aggregation than heparin.

Direct thrombin inhibitors such as bivalirudin, desirudin, and lepirudin are also used.

Described in this chapter are

Ardeparin, p.864	Lepirudin, p.945
Argatroban, p.864	Low-molecular-weight Heparins, p.949
Bemiparin, p.867	Melagatran, p.952
Bivalirudin, p.875	Nadroparin, p.963
Certoparin, p.882	Parnaparin, p.978
Dalteparin, p.891	Reviparin, p.995
Desirudin, p.892	Tinzaparin, p.1013
Enoxaparin, p.910	Ximelagatran, p.952
Heparin, p.927	
Hirudin, p.931	

The term *heparinoid* includes heparin derivatives and has also been used more loosely to include naturally occurring and synthetic highly sulfated polysaccharides of similar structure, such as danaparoid and dermatan sulfate. Some compounds have been described in many ways; some of the terms used include sulfated glucosaminoglycans, glycosaminoglycan polysulfate compounds, or sulfated mucopolysaccharides.

Described in this chapter are

Danaparoid, p.891	Sodium Apolate, p.1000
Dermatan Sulfate, p.892	Suleparoid, p.1009
Pentosan Polysulfate Sodium, p.979	Sulodexide, p.1009

Indirect anticoagulants

Indirect anticoagulants act by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. Warfarin, a coumarin, is the main drug used, but indanediones such as phenindione are also available. Since they act indirectly, they have no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is observed. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Described in this chapter are

Acenocoumarol, p.848	Fluindione, p.918
Anisindione, p.863	Phenindione, p.981
Dicoumarol, p.894	Phenprocoumon, p.981
Ethyl Biscoumacetate, p.914	Tioclomarol, p.1013
	Warfarin, p.1022

Antiplatelet drugs

Platelet aggregation is important in haemostasis (p.735) and is also involved in thrombus formation, particularly in the arterial circulation. Antiplatelet drugs reduce platelet aggregation and are used to prevent further thromboembolic events in patients who have suffered myocardial infarction, ischaemic stroke or transient ischaemic attacks, or unstable angina, and for primary prevention of a thromboembolic event in patients at risk. Some are also used for the prevention of reocclusion or restenosis following angioplasty and bypass procedures.

Antiplatelet drugs act through a wide range of mechanisms. Aspirin (p.15) is the most widely used and studied; it acts by irreversibly inhibiting platelet cyclo-oxygenase and thus preventing synthesis of thromboxane A_2. Reversible cyclo-oxygenase inhibitors such as indobufen are also available, and thromboxane synthase inhibitors and thromboxane receptor antagonists have also been used.

Drugs that interfere with adenosine metabolism have an antiplatelet effect and those used include some prostaglandins, which act by increasing platelet cyclic adenosine monophosphate levels; the thienopyridines clopidogrel and ticlopidine, which interfere with adenosine diphosphate mediated platelet activation; and the adenosine reuptake inhibitor dipyridamole.

Thrombin inhibitors such as heparin and the hirudins have antiplatelet and anticoagulant effects. Glycoprotein IIb/IIIa-receptor antagonists, such as abciximab, eptifibatide, and tirofiban, interfere with the final step in platelet aggregation and are used in unstable angina and as adjuncts in reperfusion and revascularisation procedures.

Described in this chapter are

Abciximab, p.841	Orbofiban, p.977
Cilostazol, p.884	Picotamide, p.982
Clopidogrel, p.888	Sarpogrelate, p.996
Cloricromen, p.889	Sibrafiban, p.996
Dipyridamole, p.903	Ticlopidine, p.1011
Ditazole, p.905	Tirofiban, p.1013
Eptifibatide, p.912	Trapidil, p.1016
Indobufen, p.939	Triflusal, p.1017
Lamifiban, p.944	Xemilofiban, p.1029

References.

1. Schrör K. Antiplatelet drugs: a comparative review. *Drugs* 1995; 50: 7–28.
2. Chong PH. Glycoprotein IIb/IIIa receptor antagonists in the management of cardiovascular diseases. *Am J Health-Syst Pharm* 1998; 55: 2363–86.
3. Gershlick AH. Antiplatelet therapy. *Hosp Med* 2000; 61: 15–23.
4. Scheine MS, Jang I-K. The use of glycoprotein IIb/IIIa inhibitors in patients with coronary artery disease. *Am J Med* 2000; 109: 224–37.

Beta blockers

Beta blockers are competitive antagonists at beta-adrenergic receptor sites and are used in the management of cardiovascular disorders such as hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, and heart failure. They are also given to control symptoms of sympathetic overactivity in alcohol withdrawal, anxiety states, hyperthyroidism, and tremor and in the prophylaxis of migraine and of bleeding associated with portal hypertension. Some beta blockers are used as eye drops to reduce raised intra-ocular pressure in glaucoma and ocular hypertension. Their actions and uses are discussed in more detail on p.868.

Described in this chapter are

Acebutolol, p.848	Labetalol, p.943
Alprenolol, p.856	Landiolol, p.945
Amosulalol, p.862	Levobetaxolol, p.946
Arotinolol, p.865	Levobunolol, p.946
Atenolol, p.865	Mepindolol, p.952
Befunolol, p.867	Metipranolol, p.955
Betaxolol, p.873	Metoprolol, p.956
Bevantolol, p.873	Nadolol, p.963
Bisoprolol, p.875	Nebivolol, p.964
Bopindolol, p.875	Nipradilol, p.973
Bucindolol, p.877	Oxprenolol, p.978
Bunitrolol, p.878	Penbutolol, p.979
Bupranolol, p.878	Pindolol, p.983
Carazolol, p.880	Propranolol, p.989
Carteolol, p.880	Sotalol, p.1001
Carvedilol, p.881	Talinolol, p.1009
Celiprolol, p.881	Tertatolol, p.1011
Esmolol, p.913	Timolol, p.1012
Indenolol, p.939	

Calcium-channel blockers

The main use of calcium-channel blockers is in the management of angina pectoris and hypertension; some are also employed in cardiac arrhythmias.

Calcium-channel blockers, (calcium antagonists, calcium-entry blockers, or slow-channel blockers) inhibit the cellular influx of calcium that is responsible for maintenance of the plateau phase of the action potential. Thus calcium-channel blockers primarily affect tissues in which depolarisation is dependent upon calcium rather than sodium influx, such as vascular smooth muscle, myocardial cells, and cells within the sino-atrial (SA) and atrioventricular (AV) nodes. The main actions of the calcium-channel blockers include dilatation of coronary and peripheral arteries and arterioles with little or no effect on venous tone, a negative inotropic action, reduction of heart rate, and slowing of AV conduction. However, the effects of individual drugs, and therefore their uses, are modified by their selectivity of action at different tissue sites and by baroreceptor reflexes.

Traditionally, calcium-channel blockers have been classified according to their chemical structure; other methods of classification relate to the subtypes of calcium channels which they block, and their effects on heart rate. There are three major groups that are highly specific blockers of calcium channels.

Dihydropyridine calcium-channel blockers (such as nifedipine) act on slow, L-type channels. They have a greater selectivity for vascular smooth muscle than for myocardium and therefore their main effect is vasodilatation. They are non-rate-limiting, with little or no action at the SA or AV nodes, and negative inotropic activity is rarely seen at therapeutic doses. They are used for their antihypertensive and anti-anginal properties. Some dihydropyridine derivatives, for example nimodipine, cross the blood-brain barrier and are used in cerebral ischaemia.

Benzothiazepine calcium-channel blockers (such as diltiazem) and phenylalkylamine calcium-channel blockers (such as verapamil) also act on L-type channels but they have less selective vasodilator activity than dihydropyridine derivatives. They are classed as rate-limiting and have a direct effect on myocardium, causing depression of SA and AV nodal conduction. They are used for their antiarrhythmic, anti-anginal, and antihypertensive properties.

Drugs acting principally on the fast T-type calcium channels have also been investigated. Mibefradil, a benzimidazolyl-substituted tetraline derivative, is an example of this class. It is rate-limiting, and causes coronary and peripheral vasodilatation. However, it is no longer used clinically due to serious interactions with a wide range of drugs.

For further discussion of the actions and uses of the three main groups of calcium-channel blockers, see Nifedipine, p.966, Diltiazem, p.900, and Verapamil, p.1019, respectively.

Described in this chapter are

Amlodipine, p.862	Lacidipine, p.944
Aranidipine, p.864	Lercanidipine, p.946
Azelnidipine, p.866	Lidoflazine, p.946
Barnidipine, p.866	Manidipine, p.950
Benidipine, p.868	Mibefradil, p.959
Bepridil, p.868	Nicardipine, p.965
Cilnidipine, p.884	Nifedipine, p.966
Diltiazem, p.900	Nilvadipine, p.972
Efonidipine, p.909	Nimodipine, p.972
Felodipine, p.914	Nisoldipine, p.973
Gallopamil, p.922	Nitrendipine, p.973
Isradipine, p.942	Verapamil, p.1019

References.

1. Abernethy DR, Schwartz JB. Calcium-antagonist drugs. *N Engl J Med* 1999; 341: 1447–57.
2. Eisenberg MJ, *et al.* Calcium channel blockers: an update. *Am J Med* 2004; 116: 35–43.

Cardiac inotropes

Positive cardiac inotropes increase the force of contraction of the myocardium and are therefore used in the management of acute and chronic heart failure. Some inotropes also increase or decrease the heart rate (positive or negative chronotropes), provide vasodilatation (inodilators), or improve myocardial relaxation (positive lusitropes), and these additional properties influence the choice of drug in specific situations. Drugs that are used predominantly for their inotropic effects include the cardiac glycosides and phosphodiesterase inhibitors; sympathomimetics are employed as inotropes but also have other important uses.

References.

1. Feldman AM. Classification of positive inotropic agents. *J Am Coll Cardiol* 1993; 22: 1223–7.
2. Cuthbertson BH, *et al.* Inotropic agents in the critically ill. *Br J Hosp Med* 1996; 56: 386–91.

Cardiac glycosides, such as digoxin, possess positive inotropic activity, which is mediated by inhibition of sodium-potassium adenosine triphosphatase (Na/K-ATPase). They also reduce conductivity in the heart, particularly through the atrioventricular node, and therefore have a negative chronotropic effect. The cardiac glycosides have very similar pharmacological effects but differ considerably in their speed of onset and duration of action. They are used to slow the heart rate in supraventricular arrhythmias, especially atrial fibrillation, and are also given in chronic heart failure.

Described in this chapter are

Acetyldigoxin, p.851	Digoxin, p.895
Deslanoside, p.893	Lanatoside C, p.945
Digitalis Lanata Leaf, p.894	Metildigoxin, p.955
Digitalis Leaf, p.894	Ouabain, p.977
Digitoxin, p.894	Proscillaridin, p.990
	Strophanthin-K, p.1009

Phosphodiesterase inhibitors are potent inotropes; they also have vasodilator effects. They are used in the short-term treatment of severe heart failure; long-term oral therapy with some phosphodiesterase inhibitors has been associated with increased mortality.

Described in this chapter are

Amrinone, p.862	Olprinone, p.976
Enoximone, p.911	Pimobendan, p.983
Milrinone, p.959	Vesnarinone, p.1022

Centrally acting antihypertensives

Centrally acting antihypertensives include $alpha_2$-adrenoceptor agonists such as clonidine and methyldopa. Stimulation of $alpha_2$ adrenoceptors in the CNS results in a reduction in sympathetic tone and a fall in blood pressure. Heart rate is also reduced. They are used in the management of hypertension, although other drugs with fewer adverse effects are generally preferred. Some have a role in the management of glaucoma.

Described in this chapter are

Apraclonidine, p.864	Guanfacine, p.927
Brimonidine, p.876	Methyldopa, p.953
Clonidine, p.885	Moxonidine, p.962
Guanabenz, p.926	Rilmenidine, p.996

Diuretics

Diuretics promote the excretion of water and electrolytes by the kidneys. They are used in the treatment of heart failure or in hepatic, renal, or pulmonary disease when salt and water retention has resulted in oedema or ascites. Diuretics are also used, either alone, or in association with other drugs, in the treatment of hypertension, although the mechanism for their antihypertensive effect is poorly understood.

The principal groups of diuretics are as follows.

Carbonic anhydrase inhibitors are weak diuretics and are used mainly to reduce raised intra-ocular pressure.

Described in this chapter are

Acetazolamide, p.849	Dorzolamide, p.908
Brinzolamide, p.877	Methazolamide, p.953
Diclofenamide, p.894	

'Loop' or 'high-ceiling' diuretics produce an intense, dose-dependent diuresis of relatively short duration.

Described in this chapter are

Azosemide, p.866	Furosemide, p.919
Bumetanide, p.877	Piretanide, p.983
Etacrynic Acid, p.913	Torasemide, p.1015
Etozolin, p.914	

Osmotic diuretics raise the osmolality of plasma and renal tubular fluid. They are used to reduce or prevent cerebral oedema, to reduce raised intra-ocular pressure, and in acute renal failure.

Described in this chapter are

Isosorbide, p.941	Mannitol, p.950

Potassium-sparing diuretics have a relatively weak diuretic effect and are normally used in conjunction with thiazide or loop diuretics. Canrenone, eplerenone, potassium canrenoate, and spironolactone are aldosterone antagonists and are particularly used in conditions where aldosterone contributes to the pathophysiology.

Described in this chapter are

Amiloride, p.858	Potassium Canrenoate, p.984
Canrenone, p.879	Spironolactone, p.1003
Eplerenone, p.911	Triamterene, p.1016

Thiazides (benzothiadiazines), such as bendroflumethiazide and hydrochlorothiazide, and certain other compounds, such as metolazone, with structural similarities to the thiazides, inhibit sodium and chloride reabsorption in the kidney tubules and produce a corresponding increase in potassium excretion.

Described in this chapter are

Althiazide, p.858	Hydroflumethiazide, p.937
Benzetizide, p.867	Indapamide, p.938
Bendroflumethiazide, p.867	Mebutizide, p.951
Benzthiazide, p.868	Mefruside, p.951
Butizide, p.878	Methyclothiazide, p.953
Chlorothiazide, p.882	Meticrane, p.955
Chlortalidone, p.882	Metolazone, p.956
Clopamide, p.888	Polythiazide, p.984
Cyclopenthiazide, p.890	Quinethazone, p.991
Cyclothiazide, p.891	Teclothiazide, p.1010
Epitizide, p.911	Trichlormethiazide, p.1017
Hydrochlorothiazide, p.933	Tripamide, p.1018
	Xipamide, p.1029

Ganglion blockers

Ganglion blockers are nicotinic antagonists that inhibit the transmission of nerve impulses in both sympathetic and parasympathetic ganglia. Their antihypertensive action is due to sympathetic blockade, which produces peripheral vasodilatation; there is also a direct vasodilator effect on peripheral blood vessels.

Described in this chapter are

Azamethonium, p.866	Trimetaphan, p.1017
Mecamylamine, p.951	

Lipid regulating drugs

Lipid regulating drugs are used to modify blood lipid concentrations in the management of hyperlipidaemias and for the reduction of cardiovascular risk. The principal groups of lipid regulating drugs are the statins, fibrates, bile-acid binding resins, nicotinates, and omega-3 triglycerides.

The **statins** are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme for cholesterol synthesis. They reduce cholesterol by stimulating an increase in low-density-lipoprotein (LDL)-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase high-density-lipoprotein (HDL)-cholesterol. They are generally considered to be the most effective lipid lowering drugs.

Described in this chapter are

Atorvastatin, p.866	Pitavastatin, p.984
Cerivastatin, p.881	Pravastatin, p.984
Fluvastatin, p.918	Rosuvastatin, p.996
Lovastatin, p.949	Simvastatin, p.997
Mevastatin, p.958	

The **fibrates** include derivatives of fibric acid and related compounds. They inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of very-low-density lipoproteins (VLDL); they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia.

Described in this chapter are

Bezafibrate, p.873	Fenofibrate, p.915
Ciprofibrate, p.884	Gemfibrozil, p.923
Clinofibrate, p.884	Pirifibrate, p.984
Clofibrate, p.884	Simfibrate, p.997
Etofylline Clofibrate, p.914	Tocofibrate, p.1015

Bile-acid binding resins (bile-acid sequestrants) lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting primarily in a reduction of LDL-cholesterol.

Described in this chapter are

Colesevelam, p.889	Colestyramine, p.889
Colestilan, p.889	Colextran, p.890
Colestipol, p.889	Divistyramine, p.905

Nicotinates include nicotinic acid (p.1441) and its derivatives. Nicotinic acid is a member of the vitamin B group and, in high doses, has beneficial effects on blood lipids; it reduces triglycerides and increases HDL-cholesterol, and may also modestly reduce LDL-cholesterol. Nicotinates are mainly used in hypertriglyceridaemia. Compounds derived from both nicotinic acid and clofibrate (nicotinate-fibrate derivatives) are also used.

Described in this chapter are

Acipimox, p.851	Nicofibrate, p.965
Binifibrate, p.875	Pirozadil, p.984
Etofibrate, p.914	Ronifibrate, p.996
Niceritrol, p.965	Tocoferil Nicotinate, p.1015

Omega-3 triglycerides are long-chain polyunsaturated fatty acids that primarily reduce triglycerides.

Described in this chapter are
Omega-3 Triglycerides, p.976

Nitrates

Nitrates are peripheral and coronary vasodilators used in the management of angina pectoris, heart failure, and myocardial infarction. Some of them may also be used to control blood pressure during surgery. Nitrates are believed to exert their vasodilator effect through release of nitric oxide (p.973), which causes stimulation of guanylate cyclase in the vascular smooth muscle cells; this results in an increase in cyclic guanosine monophosphate. This nucleotide induces relaxation, probably by lowering the free calcium concentration in the cytosol. Nitrates are thus termed nitrovasodilators. In their action on vascular muscle, venous dilatation predominates over dilatation of the arterioles. Venous dilatation decreases venous return as a result of venous pooling, and lowers left ventricular diastolic volume and pressure (termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequent effect is a reduction in the determinants of myocardial oxygen demand. The effect on preload is not shared by beta blockers or calcium-channel blockers. Nitrates also have a coronary vasodilator effect which improves regional coronary blood flow to ischaemic

areas resulting in improved oxygen supply to the myocardium.

Described in this chapter are
- Eritityl Tetranitrate, p.913
- Glyceryl Trinitrate, p.923
- Isosorbide Dinitrate, p.941
- Isosorbide Mononitrate, p.942
- Linsidomine, p.946
- Molsidomine, p.961
- Pentaerithrityl Tetranitrate, p.979
- Propatylnitrate, p.989
- Sodium Nitroprusside, p.1000
- Tenitramine, p.1010

Potassium-channel openers

Potassium-channel openers (potassium-channel activators) have been used in the management of hypertension; nicorandil is used in angina pectoris. They have a direct relaxant effect on smooth muscle. They act at potassium channels to allow cellular efflux of potassium which hyperpolarises the cell membrane and leads to a reduction in intracellular calcium. The reduction in intracellular calcium produces relaxation of smooth muscle. Activation of potassium channels in blood vessels produces vasodilatation. Potassium-channel openers may also have potential use in other conditions caused by smooth muscle contraction, for example asthma and urinary incontinence.

Described in this chapter are
- Cromakalim, p.890
- Nicorandil, p.965
- Pinacidil, p.983

Sympathomimetics

Sympathomimetics produce either direct or indirect stimulation of adrenergic receptors and have various actions depending on the specific receptors involved. Stimulation of $alpha_1$ receptors produces smooth muscle contraction. In the cardiovascular system this leads to vasoconstriction and increased blood pressure and in the eye to mydriasis. Other affected organs include the urinary sphincter and uterus. Stimulation of $beta_1$ receptors has an inotropic effect and also increases heart rate. Stimulation of $beta_2$ receptors leads to smooth muscle relaxation and produces vasodilatation.

Sympathomimetics have a wide range of uses. In cardiovascular disorders, they are mainly used for their $alpha_1$ and $beta_1$ properties to provide haemodynamic support in the management of acute heart failure and shock. Some sympathomimetics with alpha-agonist activity, such as phenylephrine (p.1126), pseudoephedrine (p.1129), and naphazoline (p.1124), are used to produce vasoconstriction of the nasal mucosa for the symptomatic relief of nasal congestion. Apraclonidine (p.864) and brimonidine (p.876) are examples of drugs with $alpha_2$ agonist-properties that are used to lower intra-ocular pressure and treat glaucoma.

For further discussion of the actions of sympathomimetics in general, see Adrenaline, p.852.

Described in this chapter are
- Adrenaline, p.852
- Amezinium, p.858
- Arbutamine, p.864
- Denopamine, p.892
- Dimetofrine, p.903
- Dobutamine, p.905
- Docarpamine, p.906
- Dopamine, p.907
- Dopexamine, p.908
- Etilefrine, p.914
- Gepefrine, p.923
- Ibopamine, p.937
- Isoprenaline, p.940
- Mephentermine, p.952
- Metaraminol, p.952
- Methoxamine, p.953
- Midodrine, p.959
- Noradrenaline, p.974
- Norfenefrine, p.975
- Octodrine, p.975
- Oxedrine, p.977
- Oxilofrine, p.977
- Pholedrine, p.982
- Prenalterol, p.986
- Xamoterol, p.1029

Thrombolytics

Thrombolytics are used in the treatment of thromboembolic disorders such as myocardial infarction, peripheral arterial thromboembolism, and venous thromboembolism (deep-vein thrombosis and pulmonary embolism), and some may be used in ischaemic stroke. They are also used to clear blocked cannulas and shunts.

Thrombolytics activate plasminogen to form plasmin, a proteolytic enzyme that degrades fibrin and thus produces dissolution of clots. Some thrombolytics, such as alteplase, act only on fibrin-bound plasminogen and have little effect on circulating, unbound plasminogen; these thrombolytics are termed fibrin-specific agents. Thrombolytics, such as streptokinase, that affect circulating, unbound as well as fibrin-bound plasminogen are termed fibrin-nonspecific agents. Although it has been suggested that the degree of fibrin specificity should influence the risk of haemorrhage, the clinical significance of this has not been established (see Haemorrhage under Adverse Effects of Streptokinase, p.1006).

Described in this chapter are
- Alteplase, p.857
- Anistreplase, p.863
- Defibrotide, p.892
- Duteplase, p.909
- Fibrinolysin, p.916
- Lanoteplase, p.945
- Monteplase, p.961
- Nasaruplase, p.964
- Nateplase, p.964
- Pamiteplase, p.978
- Plasminogen, p.984
- Reteplase, p.995
- Saruplase, p.996
- Staphylokinase, p.1005
- Streptokinase, p.1005
- Tenecteplase, p.1010
- Urokinase, p.1018

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Vasodilators

Vasodilator is a broad term applied to a wide range of drugs that produce dilatation of blood vessels. The main groups of drugs producing vasodilatation are ACE inhibitors (p.842), nitrates (above), and direct-acting vasodilators.

Direct-acting vasodilators act predominantly on the arterioles reducing peripheral resistance and producing a fall in blood pressure. Their main use is in hypertension, although other drugs are generally preferred. Some of them are used in hypertensive crises.

Described in this chapter are
- Cadralazine, p.878
- Diazoxide, p.893
- Dihydralazine, p.899
- Endralazine, p.910
- Hydralazine, p.931
- Minoxidil, p.960
- Todralazine, p.1015
- Tolazoline, p.1015

Other vasodilators may be divided into those used for ischaemic heart disease and those used mainly for cerebral and peripheral vascular disorders. Some drugs originally regarded as vasodilators and used for cerebral and peripheral vascular disorders are now thought to improve microcirculatory flow disturbances by altering the rheological properties of blood or tissue metabolism.

Vasodilators used in Ischaemic Heart Disease

Described in this chapter are
- Carbocromen, p.880
- Cinepazet, p.884
- Cloridarol, p.889
- Dilazep, p.900
- Etafenone, p.914
- Fendiline, p.915
- Hexobendine, p.931
- Oxyfedrine, p.978
- Trapidil, p.1016
- Trimetazidine, p.1018

Vasodilators used in Cerebral and Peripheral Vascular Disorders

Described in this chapter are
- Azapetine, p.866
- Bamethan, p.866
- Bencyclane, p.867
- Buflomedil, p.877
- Butalamine, p.878
- Calcitonin Gene-related Peptide, p.878
- Cetiedil, p.882
- Cinepazide, p.884
- Cyclandelate, p.890
- Di-isopropylammonium Dichloroacetate, p.900
- Fasudil, p.914
- Ifenprodil, p.938
- Inositol Nicotinate, p.939
- Naftidrofuryl, p.964
- Nicotinyl Alcohol, p.966
- Pentifylline, p.979
- Pentoxifylline, p.979
- Piprateçol, p.983
- Propentofylline, p.989
- Raubasine, p.994
- Xantinol Nicotinate, p.1029

Management of Cardiovascular Disorders

Management of the main cardiovascular disorders is discussed below. These overviews focus on pharmacological therapy, but other options are also mentioned where they form an important part of treatment.

Advanced cardiac life support

Cardiac arrest is the cessation of effective cardiac mechanical activity and is usually a result of ischaemic heart disease in adults and respiratory or circulatory failure in children. It may be associated with four arrhythmias, namely ventricular fibrillation, pulseless ventricular tachycardia, asystole, and electromechanical dissociation (pulseless electrical activity). Ventricular fibrillation is the commonest in adults and asystole in children. In ventricular fibrillation and pulseless ventricular tachycardia there is chaotic electrical and mechanical activity; in asystole a total absence of both activities; and in electromechanical dissociation an absence of mechanical activity, or undetectable activity, in the presence of some electrical activity.

Cardiac arrest is an emergency situation[1,2] and should be treated with full life support measures.

International guidelines[3] for advanced life support and the immediate period of cardiac arrest have been published, developed by the American Heart Association in collaboration with various resuscitation councils, including the International Liaison Committee on Resuscitation. European[4] and UK[5] guidelines have also been published; these are based on the international guidelines and, apart from some differences in detail, are broadly similar.

In order to maintain cardiorespiratory function, basic life support (cardiopulmonary resuscitation) consisting of chest compression and ventilation (mouth-to-mouth/mask) should be started immediately and continued during the resuscitation attempt. Subsequent procedures will depend to some extent on the type of arrhythmia present. For the commonest, ventricular fibrillation, rapid defibrillation is of paramount importance and should not be delayed by other necessary measures such as the administration of oxygen, intubation, and the provision of intravenous access. Defibrillation is intended to produce momentary asystole and allow the natural pacemakers to resume normal activity. Adrenaline is given principally to increase the efficacy of basic life support rather than as an adjunct to defibrillation although evidence that it improves survival is limited; through its alpha agonist effects it increases myocardial and cerebral blood flow. A dose of 1 mg of adrenaline is regarded as the 'standard' dose. A higher dose of 5 mg has been used in some clinical trials, but there is no evidence that this dose is associated with an improvement in overall survival rate and it is not generally recommended. Vasopressin has been tried as an alternative although it has not been shown to be superior to adrenaline.[6,7] In the case of asystole, atropine may be given to block excess vagal tone. Amiodarone may be considered for ventricular tachycardia or fibrillation; lidocaine or procainamide are alternatives if amiodarone is not available. A study[8] comparing lidocaine with amiodarone for shock-resistant ventricular fibrillation found that survival to hospital admission was higher in those given amiodarone. Survival to discharge was not increased, however, but the study was not powered to assess this outcome. Other drugs that may be given during resuscitation attempts include buffering agents such as intravenous sodium bicarbonate for acidosis, and calcium, magnesium, or potassium salts for known deficiencies. Therapeutic hypothermia may be beneficial in patients who remain unconscious following resuscitation, and cooling to 32° to 34° has been recommended[9] in unconscious adults whose initial rhythm was ventricular fibrillation. Specific guidelines for the different types of arrhythmia are as follows.

Ventricular fibrillation and pulseless ventricular tachycardia are treated in the same way. The guidelines for adults emphasise that the first defibrillating shock must be administered as quickly as possible. In cases of witnessed cardiac arrest a precordial thump, which sometimes aborts the arrhythmia if given within 30 seconds of the loss of cardiac output, may be given before attaching the monitor/defibrillator, but the attachment of the defibrillator must not be delayed. The initial monophasic direct current shock (200J) is followed as necessary by a second (200J) and a third (360J) shock if the preceding shock is not successful; lower energies may be used for biphasic shocks. If the initial group of three shocks is unsuccessful, chest compression and ventilation should be continued and further shocks given. Adrenaline 1 mg intravenously should be administered before the next set of three shocks (each of 360J) but should not delay further defibrillation. Endotracheal administration of adrenaline may be used if intravenous access cannot be obtained. Doses 2 to 3 times greater than those given intravenously are suggested, although studies investigating this route have had mixed results.[10,11] A single dose of vasopressin (as argipressin) 40 units intravenously has been suggested[3] as an alternative to adrenaline, followed by further doses of adrenaline if required, but this is not universally recommended.[4,5] The cycle of adrenaline and up to three shocks (360J or equivalent) should be repeated as necessary. Amiodarone or other antiarrhythmics may be considered after the first cycle, provided that administration does not delay further shocks. Other drugs (such as those described above) may be used as appropriate. Meanwhile, the adrenaline and 3-shock cycles continue for as long as defibrillation is indicated. The total number of cycles is a matter of judgement but a resuscitation attempt may reasonably last for anything from 10 minutes to 1 hour.

Ventricular fibrillation in children is unusual; the basic management is the same as in adults, but the energies used for defibrillation and the doses of drugs used are different and a precordial thump is not generally given. The initial dose of adrenaline is 10 micrograms/kg by intravenous or intraosseous injection; for the second and subsequent dos-

es; a higher dose of 100 micrograms/kg may be considered, although there is no evidence that this improves outcome. Endotracheal administration is an alternative route if an intravenous or intraosseous access cannot be obtained; the suggested endotracheal dose is 100 micrograms/kg for both initial and subsequent doses.

In survivors of ventricular fibrillation and pulseless ventricular tachycardia in whom it is considered there is a high risk of recurrence, implantable cardioverter defibrillators may be used. Drug therapy may also be used prophylactically (see Ventricular Tachycardia under Cardiac Arrhythmias, p.816).

Asystole and electromechanical dissociation have a much less favourable prognosis than ventricular fibrillation or pulseless ventricular tachycardia, although there are certain causes such as hypovolaemia, hypoxia, pneumothorax, pulmonary embolism, drug overdose, hypothermia, and electrolyte imbalances that may respond to treatment and these should be considered and the appropriate therapy given promptly once resuscitation has been instituted. As described above, a precordial thump may be appropriate if the cardiac arrest is witnessed. Once ventricular fibrillation or tachycardia is positively excluded, cardiopulmonary resuscitation should be instituted immediately and adrenaline 1 mg should be given intravenously every 3 to 5 minutes. In asystole a single dose of atropine 3 mg intravenously is also administered to block vagal activity.[4,5] In the international guidelines[3] atropine is recommended in repeated doses of 1 mg to a total of 0.04 mg/kg rather than as a single dose of 3 mg. Other drugs (such as buffering agents) may be considered. Cardiac pacing may be instituted once there is evidence of electrical activity. Resuscitation should generally continue for at least 20 to 30 minutes from the time of collapse; prolonged resuscitation is not usually undertaken as recovery rarely occurs after 15 minutes of asystole if there has been no response.

For children with asystole or electromechanical dissociation, the initial dose of adrenaline recommended is 10 micrograms/kg given by intravenous or intraosseous injection; as for ventricular fibrillation, higher doses have been used subsequently but are not generally recommended. Adrenaline may be given by the endotracheal route in doses of 100 micrograms/kg. Atropine is not generally used and a precordial thump is not recommended.

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Angina pectoris

Angina pectoris is a syndrome that arises from an inadequate myocardial oxygen supply (myocardial ischaemia) and is part of the spectrum of coronary or ischaemic heart disease. The prominent symptom is transient precordial discomfort ranging from a mild ache to severe pain. Some patients may also experience dyspnoea, nausea, sweating, and left arm discomfort. Myocardial oxygen supply depends upon coronary blood flow, which normally increases to meet increased oxygen demands. Ischaemia occurs when blood flow either cannot be increased, or is reduced; this may be due to a fixed obstruction in the coronary arteries, vasoconstriction, thrombus formation, or platelet aggregation.

Three main types of angina have been described: stable angina; unstable angina; and Prinzmetal's angina. Although these are discrete groups, stable angina may become unstable, and Prinzmetal's angina may co-exist with stable or unstable angina.

Stable angina (effort angina) is angina which is usually precipitated by exertion and relieved by rest. It is often called chronic stable angina and as the name implies the frequency, intensity, and duration of the attacks are stable. The predominant underlying disorder is coronary atherosclerosis causing a fixed obstruction in one or more coronary arteries. While the restricted coronary blood flow is still adequate for oxygenation of the unstressed heart, it is not capable of being increased to meet the increase in myocardial oxygen demand that may occur during exercise, cold exposure, emotional stress, or after eating.

Unstable angina is an acute coronary syndrome intermediate between stable angina pectoris and myocardial infarction. Three subgroups are recognised: angina that presents from the beginning as severe and frequent attacks; an increase in the frequency, intensity, and/or duration of previously stable angina, often with diminishing responsiveness to sublingual nitrates (crescendo angina); and recurring or prolonged angina at rest. In unstable angina the decreased coronary artery blood flow is usually caused by disruption of an atherosclerotic plaque, which leads to platelet adhesion and aggregation, thrombus formation, and vasoconstriction, thus resulting in partial occlusion of one or more coronary arteries. The coronary blood flow can be so restricted that it does not meet the oxygenation demands of the unstressed heart, but the ischaemia is not sufficient to result in myocardial damage. Non-Q wave myocardial infarction is a closely related syndrome in which some myocardial injury occurs, but to a lesser extent than in acute myocardial infarction. Patients with the different acute coronary syndromes may present similarly and definitive diagnosis is only possible retrospectively once the results of biochemical measurements such as cardiac troponins or cardiac enzymes are available. However, patients without the characteristic ECG change of ST-segment elevation (non-ST elevation myocardial infarction) do not generally develop Q waves and management is as for unstable angina. Patients with unstable angina are at an increased risk of sudden death and myocardial infarction, and those with rest pain are at the greatest risk.

Prinzmetal's angina (variant angina) is a rare form of angina caused by coronary vasospasm and is often associated with atherosclerosis. It occurs spontaneously at rest and with greater frequency during the night or early hours of the morning. It is associated with transient ST-segment elevation and carries a risk of progression to myocardial infarction. Prolonged vasospasm may also lead to ventricular arrhythmias, heart block, or death.

In addition to the types of angina described above periods of **silent myocardial ischaemia** (asymptomatic transient myocardial ischaemia) in which there is no anginal pain have been identified during ECG monitoring. In some patients all ischaemic episodes are asymptomatic. However, asymptomatic ischaemic episodes also occur in patients with angina and seem to be more common than symptomatic episodes. It is not clear why some episodes of ischaemia are symptomatic while others are not.

Treatment depends on the type of angina and involves symptomatic management of acute anginal pain, antithrombotic therapy to prevent progression to myocardial infarction, and long-term management both to prevent angina attacks and to reduce the risk of other cardiovascular events. Anti-anginal treatment is used in both stable and unstable angina and is described in more detail below; it includes drug therapy (nitrates, beta blockers, calcium-channel blockers, and potassium-channel openers), percutaneous coronary interventions, and coronary artery bypass surgery. Antithrombotics are used in unstable angina and include anticoagulants and antiplatelets (see Treatment of Unstable Angina, below). Long-term measures to reduce cardiovascular risk are important in all patients, even when symptoms are controlled, and include antiplatelet therapy (which should be given to all patients unless contra-indicated), lipid lowering therapy, and lifestyle changes; these interventions are discussed in more detail under Cardiovascular Risk Reduction, p.819. Patients with ischaemic heart disease who undergo non-cardiac surgery are at risk of complications resulting from perioperative myocardial ischaemia.[1] Perioperative use of drugs such as beta blockers or mivazerol is under investigation.

Anti-anginal drugs act in a variety of ways. Glyceryl trinitrate and other organic *nitrates* have a vasodilator effect with venodilatation predominating over dilatation of the arterioles. Dilatation of veins decreases venous return as a result of venous pooling and lowers left ventricular diastolic volume and pressure (together termed a reduction in preload). The smaller or less important dilatation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (termed a reduction in afterload). The consequence of these effects is a reduction in myocardial oxygen demand. Also the vasodilator effect improves regional coronary blood flow to ischaemic areas, and alleviates coronary spasm. *Beta blockers* cause a slowing of the heart rate and reduction in contractility and therefore reduce myocardial oxygen demand. *Calcium-channel blockers* reduce the work of the heart by dilating peripheral arteries, and diltiazem and verapamil also slow the heart rate. Calcium-channel blockers also act on the coronary circulation preventing spasm. *Potassium-channel openers* act as coronary vasodilators, while nicorandil also has a nitrate component that may contribute to its effect.

Percutaneous transluminal coronary *angioplasty* is a means of mechanically dilating coronary arteries using a balloon that has been passed down a catheter and inflated at the appropriate sites, and is often used in conjunction with stenting. Nitrates and calcium-channel blockers may be given to alleviate coronary spasm due to the procedure. Coronary artery *bypass surgery* uses a vein or artery graft to bypass the occlusion. Both angioplasty and bypass surgery abolish or reduce episodes of angina in most patients but symptoms commonly recur over a period of time due to restenosis. Adjunctive therapy is therefore needed both to prevent short-term thromboembolic complications and long-term reocclusion (see Reperfusion and Revascularisation Procedures, p.834). Other interventions that have been tried in refractory angina include transmyocardial revascularisation and spinal cord stimulation.

Treatment of stable angina. Management of the patient with stable angina[2-6] primarily involves the use of anti-anginal drugs, antiplatelet therapy, and measures to reduce cardiovascular risk. Any contributory conditions, such as anaemia, should be identified and treated.

Treatment of infrequent angina episodes (less than about 2 attacks per week) usually consists of glyceryl trinitrate given when required, generally sublingually; alternatively, a buccal tablet or spray formulation may be used. Isosorbide dinitrate, in the form of sublingual tablets or spray, may be used, although it has a slower onset of action than glyceryl trinitrate. Glyceryl trinitrate in sublingual or buccal forms may also be used before an activity or circumstance that might precipitate an attack.

When episodes occur more frequently, sublingual glyceryl trinitrate, at least on its own, may no longer be appropriate, and regular symptomatic treatment has to be considered. Choice depends upon patient characteristics and any concurrent medical conditions.

Beta blockers are the mainstay of therapy. They are generally considered to be first-line treatment if sublingual glyceryl trinitrate is not adequate since they provide effective symptom control and have also been shown to reduce mortality in certain patients with high cardiovascular risk.[2,4,5] The different beta blockers appear to be equally effective in stable angina, although it has been suggested[7] that those with intrinsic sympathomimetic activity should be avoided.

A calcium-channel blocker may be used as an alternative, particularly in patients unable to tolerate beta blockers. Care is required in selecting an appropriate drug since the properties of dihydropyridine calcium-channel blockers (such as nifedipine) and rate-limiting calcium-channel blockers (diltiazem and verapamil) are not the same. Studies comparing long-acting calcium-channel blockers (verapamil[8] or modified-release nifedipine[9]) with beta blockers have shown similar outcomes in terms of symptom control and cardiovascular events. However, dihydropyridines may cause tachycardia and are less suitable than rate-limiting calcium-channel blockers for monotherapy; they should not be used without beta blockers in unstable angina.[3] Short-acting preparations of nifedipine have been associated with increased mortality and are not recommended (see under Adverse Effects of Nifedipine, p.966).

Regular nitrate therapy is a further alternative, and includes modified-release forms of glyceryl trinitrate, for example transdermal patches, and the long-acting nitrates such as isosorbide dinitrate or isosorbide mononitrate; it may be particularly suitable in patients with left ventricular dysfunction. Diminished effectiveness or tolerance occurs, particularly with nitrate preparations that produce sustained plasma concentrations, and dosage regimens including a nitrate-free period should be used (see Nitrate Tolerance, p.924).

[redacted]

Alternative drugs that may be used as monotherapy in the management of stable angina include potassium-channel openers such as nicorandil.

Where optimal therapy with a single drug fails to control symptoms, combination therapy may be used. There is additional benefit from concomitant nitrate and beta blocker therapy, since nitrates can moderate the excessive effects that beta blockers may have in increasing left ventricular diastolic volume and pressure and in inducing bradycardia. Calcium-channel blockers may also be used with nitrates; the combination of verapamil or diltiazem with a nitrate may be preferable to a combination of nifedipine (or other dihydropyridine derivative) with nitrates as both nifedipine and nitrates cause reflex tachycardia, hypotension, and headaches.

Combination therapy with beta blockers and dihydropyridine calcium-channel blockers or diltiazem improves exercise tolerance[2] but adverse effects may be a problem. Verapamil should be avoided in such combinations as its use with a beta blocker increases the risk of impaired cardiac conduction (see p.1020). Caution with any combination of a calcium-channel blocker with a beta blocker is particularly necessary in patients with pre-existing conduction disorders or moderate to severe left ventricular dysfunction as the use of calcium-channel blockers may actually increase mortality.[10]

Triple therapy using a nitrate, a beta blocker, and a calcium-channel blocker may sometimes be used although it is likely to be associated with more adverse effects.

If medical treatment does not control the angina the patient should be investigated to determine suitability for coronary angioplasty or coronary artery bypass surgery.[11] Angioplasty is ideally suited to patients with single-vessel disease, good left ventricular function, and stable angina, although the technique is also used in patients with more complex disease, impaired left ventricular function, and unstable angina.[12] Coronary artery bypass surgery is generally the preferred technique in patients with disease of the left main coronary artery, three-vessel disease, or impaired left ventricular function.[13] Age and other clinical factors also influence the choice of technique; angioplasty may be favoured in the elderly and others with high operative risks.[12] The role of angioplasty in patients whose symptoms are controlled with medical treatment is less clear. A comparison of angioplasty and medical treatment in patients considered suitable for either strategy suggested that greater symptomatic improvement following angioplasty may not be maintained, and that the risk of death or non-fatal infarction may be greater than for patients receiving medical treatment alone;[14] however, quality of life may be better following angioplasty.[15]

Treatment of unstable angina. Unstable angina and non-ST segment elevation myocardial infarction are managed similarly.[16-24] Unstable angina is generally regarded as an emergency and those patients with a change in the pattern of previously stable angina or with recurring or prolonged angina at rest should be hospitalised. A resting ECG should be obtained to identify those patients with ST segment elevation who should be treated as for acute myocardial infarction (p.828). In patients without ST segment elevation, initial treatment is given to control the symptoms and reduce ischaemia and involves use of antiplatelets, heparin, nitrates, beta blockers, and possibly calcium-channel blockers. Subsequent therapy depends on the risk of progression and may involve glycoprotein IIb/IIIa inhibitors and urgent revascularisation. Once the patient has been stabilised, underlying risk factors should be identified and treated, and long-term anti-anginal therapy may be given.

Aspirin is routinely included in the initial treatment. It inhibits platelet aggregation and substantially reduces the incidence of myocardial infarction and death, although it has not been shown to reduce the number of ischaemic episodes or to relieve pain during the acute phase. Clopidogrel or ticlopidine may be alternatives if aspirin is not tolerated, although clopidogrel has fewer adverse effects and is generally preferred. Additional benefit has also been shown[25] with a combination of aspirin with clopidogrel, given for 3 to 12 months.

Heparin is generally given in addition to aspirin to reduce thrombin generation and fibrin formation. Both unfractionated heparin and low-molecular-weight heparin are of established benefit,[26-28] reducing the number of ischaemic episodes and major cardiovascular events during the acute phase, with sustained benefit in the longer term.[28] Unfractionated heparin is generally given by continuous infusion for at least 48 hours,[16,19,23] although it may also be effective subcutaneously.[29] Reactivation of unstable angina has been reported in patients discontinuing intravenous heparin;[30] combination with aspirin or gradual discontinuation may prevent this effect.[19] Low-molecular-weight heparins appear to be at least as safe and effective as unfractionated heparin and their advantages in terms of administration have led to their increasing use, although unfractionated heparin may be preferred in patients undergoing bypass surgery or percutaneous coronary intervention.[22] Prolonged use of low-molecular-weight heparins has been investigated,[31,32] but benefit has not been confirmed. Direct thrombin inhibitors such as lepirudin have also been tried;[33] compared with heparin, lepirudin led to fewer major cardiovascular events at 7 days but bleeding episodes were more common in the lepirudin group.

Nitrates are widely used although evidence from controlled trials is limited.[22,24] The initial treatment may be given intravenously to produce a fast response and to provide better dose control than can be achieved with other routes. Glyceryl trinitrate or isosorbide dinitrate are used. Generally, the intravenous route is only used during the acute phase, and once the patient is stabilised the infusion is withdrawn, usually within about 48 hours. Sublingual glyceryl trinitrate may be tried initially in patients with less severe symptoms.

Treatment with a beta blocker is started during the acute phase to reduce myocardial oxygen demand. Initially, the intravenous route may be used and then followed by oral administration. Beta blockers with intrinsic sympathomimetic activity do not reduce resting heart rate and are not recommended.[7,22,23]

Calcium-channel blockers may be added to therapy although they are generally reserved for patients with angina refractory to treatment with the above drugs. However, calcium-channel blockers are the drugs of choice if the angina has a vasospastic aetiology, for example in Prinzmetal's angina. The choice of calcium-channel blocker is described under the treatment of stable angina above.

Thrombolytics have been tried in unstable angina but do not improve outcome and are associated with an excess of bleeding complications; thrombolytic therapy is therefore not recommended in patients with unstable angina.[22,23]

Once the initial therapy has been started patients should be assessed for their risk of progressing to myocardial infarction and the need for additional treatment. Patients at high risk include those with recurrent ischaemia and those with raised cardiac troponins. Glycoprotein IIb/IIIa inhibitors such as abciximab, eptifibatide, and tirofiban are potent inhibitors of platelet aggregation and may have a role in patients at high risk. They are of established benefit in patients undergoing percutaneous coronary angioplasty (see Reperfusion and Revascularisation Procedures, p.834), but results in patients treated medically have been less consistent. A meta-analysis[34] of trials studying the efficacy of glycoprotein IIb/IIIa inhibitors in unstable angina or non-ST segment elevation myocardial infarction found that they reduced the risk of death or myocardial infarction in patients who were not scheduled for early revascularisation, particularly in those at high risk of progression, such as those with raised troponins. However, many of the patients included in the analysis did receive revascularisation and the use of glycoprotein IIb/IIIa inhibitors in patients not undergoing intervention remains questionable.[22] Whether all the glycoprotein IIb/IIIa inhibitors are effective is also unclear. Individual studies have reported beneficial results in patients receiving tirofiban and aspirin alone[35] or in combination with heparin therapy,[36] and with eptifibatide[37] in addition to standard therapy. However, a study with abciximab[38] in addition to aspirin and heparin failed to show any additional benefit.

Coronary angiography should be performed early in patients at high risk, including those in whom medical therapy fails to control symptoms, with urgent revascularisation where indicated.[39,40] In patients at lower risk, the benefits of early revascularisation are less well established; such patients should be assessed before discharge, usually with stress testing, and angiography should be performed as appropriate.

Following discharge, patients should continue to take aspirin and a beta blocker; continuation of clopidogrel for 9 months, in combination with aspirin, has also been recommended.[22,24] As in stable angina, measures to reduce cardiovascular risk should be adopted. Statins have been shown to reduce cardiovascular events when started early after admission for unstable angina,[41] or in patients with a history of unstable angina,[42] and should be considered. Some patients are given a long-acting nitrate for long-term prophylaxis, although nitrates have not been shown to protect against subsequent cardiovascular events. Long-term oral anticoagulation has been used but is not routine therapy, and studies of warfarin with aspirin have given mixed results.[43,44]

Treatment of Prinzmetal's angina. This should be treated like unstable angina with the addition of a calcium-channel blocker; the selection of an appropriate calcium-channel blocker is described above under the treatment of stable angina. Once stabilised, maintenance should include a nitrate, or calcium-channel blocker, or both to protect against further spasm. Surgery may be considered in some patients.

Treatment of silent myocardial ischaemia. Silent myocardial ischaemia has been recognised as a potential risk factor for future cardiovascular morbidity and mortality and research has been undertaken to assess whether suppressing such episodes can improve long-term outcome. Although many of the therapies used in angina reduce the incidence of silent ischaemia it is not yet clear whether complete suppression of ischaemia affects prognosis.[9,45-47] Other studies have suggested that periods of ischaemia may protect the heart during subsequent myocardial infarction[48] and further work is needed to reconcile these findings.

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considered suitable for routine prophylaxis; it may have a role if acetazolamide is unavailable or contra-indicated.[1-3] If it is used, dexamethasone should be started a few hours before ascent;[3] adverse effects may be fewer if the dose is tapered before stopping.[4]

Nifedipine has been shown to lower pulmonary artery pressure and to protect against pulmonary oedema in people susceptible to the development of pulmonary symptoms at altitude[6] but is not usually recommended for prophylaxis due to the risk of adverse effects.

Other drugs that have shown some benefit in small studies include *spironolactone*[4] and *ginkgo biloba*.[1,4] A study[7] with inhaled *salmeterol* suggested that it reduced the risk of pulmonary oedema in people considered to be at high risk. *Aspirin* was reported[8] to reduce the incidence of headache in a small study in people with a history of headache at high altitude.

Treatment. Once symptoms of altitude illness develop the course of action should be determined by the severity and nature of the symptoms.

When symptoms are *mild* and are not suggestive of pulmonary or cerebral oedema, rest and mild analgesics for headache are usually all that is required; symptoms resolve within a few days and further ascent is possible.[1-3] *Acetazolamide* may have some benefit in relieving symptoms[1,2,9] although studies have been small. If mild symptoms of pulmonary oedema are present, such as dyspnoea and cough, rest with supplementary oxygen and further oxygen at night may resolve the symptoms and allow further ascent; however signs and symptoms at altitude may be confusing and it is always safest to descend. The use of hypnotics at altitude is not generally advised since there is a risk that respiratory depression may further reduce oxygen saturation. However, a small study[10] using the short-acting benzodiazepine *temazepam* reported that sleep quality was improved without an alteration in mean oxygen saturation.

When symptoms are *moderate to severe*, and are progressing or suggestive of cerebral oedema, immediate descent is necessary.[1-3] Descending by as little as 400 to 500 metres is beneficial. Various drugs and therapies have been given to alleviate symptoms and to facilitate descent and should also be used when immediate descent is not possible. For example, *dexamethasone* can reduce the symptoms of acute mountain sickness and might be used in emergencies.[11,12] Portable hyperbaric chambers are available[13] and provide rapid but short-term improvement. They may be useful in combination with dexamethasone, which has a more sustained effect.[14]

If pulmonary oedema is present, oxygen, which relieves hypoxia and reduces pulmonary hypertension, should be given;[1-3] *nifedipine*, which suppresses the exaggerated hypoxic pulmonary vasoconstrictor response seen in people with pulmonary oedema, has provided benefit.[15] Positive-pressure expiration may also be useful;[2] it has the effect of increasing oxygen saturation and partial pressure of carbon dioxide at altitude. Inhalation of nitric oxide has also been reported to improve oxygenation but administration may not be feasible at altitude.[16]

People with cerebral oedema should be given *dexamethasone* and oxygen therapy.

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Hyperlipidaemias

Hyperlipidaemia results from a disorder in the synthesis and degradation of plasma lipoproteins. Although the main concern has generally been the overall elevation of plasma lipids (hyperlipidaemia), it is now increasingly recognised that the balance of lipids in the plasma is also important, and the term dyslipidaemia is often used. Dyslipidaemias have genetic and other causes, and are often associated with a high-fat diet. Although patients with hyperlipidaemia may have symptoms that require treatment, the major concern is their increased risk of ischaemic heart disease.

The lipids that are of relevance in hyperlipidaemias are cholesterol, an essential component of cell membranes and a precursor of steroid hormone synthesis, and triglyceride, an important energy source. They are transported in the blood as lipoproteins.

Lipoproteins are complex particles[1,2] comprising a hydrophilic coat of phospholipids, free cholesterol, and specific polypeptides termed apolipoproteins (apoproteins) around a core of varying proportions of triglyceride and of cholesterol which is present as cholesteryl ester. The lipoproteins are characterised by their density, which in general increases as they are metabolised and the proportion of cholesteryl ester to triglyceride increases. Table 1, below, lists the principal lipoproteins and their associated lipids. The lowest density lipoproteins are the chylomicrons which transport triglyceride derived from dietary fat, and the VLDL (very low-density lipoproteins; pre-β lipoproteins) which transport endogenous triglyceride mainly synthesised in the liver, to peripheral tissues. The triglyceride is hydrolysed in the peripheral tissues by lipoprotein lipase, which is activated by apolipoprotein CII present in the lipoproteins. Both chylomicrons and VLDL are progressively depleted of triglyceride, yielding increasingly dense lipoprotein particles termed 'remnant' particles. Chylomicron remnants are cleared rapidly from plasma by the liver where they are metabolised, releasing free cholesterol. VLDL remnants, which include IDL (intermediate-density lipoproteins; broad β-lipoproteins), may also be cleared by the liver or converted to LDL (low-density lipoprotein; β-lipoprotein). HDL (high-density lipoproteins; α-lipoproteins) are synthesised in the liver and small intestine and have a role in the transport of cholesterol from the peripheral tissues back to the liver, where it is either utilised or excreted in the bile as bile acids and unesterified cholesterol. The majority is reabsorbed from the intestines and a small proportion is excreted in the faeces.

Defining hyperlipidaemia is difficult due to the marked variation in lipid concentrations between different populations. Apparently 'normal' lipid concentrations may still be associated with a significant risk of cardiovascular disease, and this may depend on which lipids are affected. Epidemiological data show a progressive and continuous relationship between plasma-cholesterol concentrations and mortality from ischaemic heart disease. The Framingham Study[3] found a 9% increase in death from cardiovascular disease for each 10 mg/dL (0.26 mmol/litre) rise in total plasma-cholesterol concentration. Plasma-cholesterol concentrations of 5.2 mmol/litre (200 mg/dL) or less are associated with a low risk of ischaemic heart disease. The increased risk is due mainly to raised LDL-cholesterol. In contrast, HDL-cholesterol is inversely associated with ischaemic heart disease. Low plasma concentrations of HDL-cholesterol (below 1 mmol/litre or 40 mg/dL) are generally associated with increased risk of ischaemic heart disease, whereas high concentrations are protective.[4] There also appears to be an association between plasma-triglyceride concentrations and risk of ischaemic heart disease. Some triglyceride-rich lipoproteins such as chylomicron remnant particles and IDL are atherogenic and the risk of heart disease increases as triglyceride concentrations increase in patients who also have high total cholesterol and low HDL-cholesterol concentrations. Hypertriglyceridaemia alone (greater than 2.3 mmol/litre or 200 mg/dL) may be an independent risk factor for ischaemic heart disease, but any clinical benefit from intervention to lower triglyceride levels is yet to be established.[5] Current US guidelines[2,6] suggest an LDL-cholesterol concentration of below 100 mg/dL as optimal, and a total cholesterol concentration of below 200 mg/dL as desirable, although evidence from more recent studies suggests that even lower concentrations may be beneficial.[16] However, the absolute risk for any individual also depends on other cardiovascular risk factors, including smoking and hypertension, and treatment decisions should in general be based on assessment of overall risk (see Cardiovascular Risk Reduction, p.819).

Hyperlipidaemias may result from a number of underlying defects and various methods have been used for classification.[7] A simple system is to divide them on the basis of whether raised serum cholesterol (hypercholesterolaemia), triglyceride (hypertriglyceridaemia), or both (mixed or combined hyperlipidaemia) is the predominant abnormality. Alternatively, the Fredrickson/WHO method (see Table 2, below) describes them in terms of the lipoprotein abnormality (hyperlipoproteinaemia), although this is less useful clinically. Within these systems, primary hyperlipidaemias are those with an underlying genetic defect, whereas secondary hyperlipidaemias are caused by another disease state or by drug therapy. Primary and secondary causes of hyperlipidaemia may co-exist.

Primary hyperlipidaemias (see Table 3, p.824) may be monogenic, relating to a single genetic defect, but much more commonly they are due to the interaction of a number of genes with dietary and other factors (polygenic). Individuals with common, polygenic (multifactorial) hypercholesterolaemia tend to have only mild or moderate elevations of plasma-cholesterol, whereas those with monogenic hyperlipidaemias tend to have much higher plasma-lipid concentrations.

Secondary hyperlipidaemias may have various causes. Diseases producing hypertriglyceridaemia include diabetes mellitus, chronic renal failure, and bulimia. Hypercholesterolaemia can occur in hypothyroidism, nephrotic syndrome, biliary obstruction, and anorexia nervosa. Drugs that may produce hypertriglyceridaemia and/or hypercholesterolaemia include thiazide diuretics (in high doses), beta blockers, corticosteroids, and antivirals in patients with HIV infection. Excessive alcohol intake may produce elevated plasma-triglyceride concentrations.

The degree of hyperlipidaemia seen in patients with either primary or secondary hyperlipidaemia is influenced by various factors, including, importantly, diet. A diet rich in saturated fat and cholesterol and poor in fibre can produce hypercholesterolaemia. Obesity further predisposes to hyperlipidaemia. Other factors that may influence lipid concentrations include pregnancy, lack of exercise, and smok-

Table 1. Principal lipoproteins and associated lipids.

Lipoprotein	Lipid
Chylomicron	Triglyceride
VLDL	Triglyceride
IDL	Cholesterol and triglyceride
LDL	Cholesterol
HDL	Cholesterol

Table 2. Classification of hyperlipoproteinaemias.

		Plasma lipids affected	
WHO classification	Lipoproteins elevated	Cholesterol	Triglyceride
I	Chylomicrons	Normal or elevated	Elevated
IIa	LDL	Elevated	Normal
IIb	LDL and VLDL	Elevated	Elevated
III	VLDL with abnormally high cholesterol content	Elevated	Elevated
IV	VLDL	Normal or elevated	Elevated
V	Chylomicrons and VLDL	Elevated	Elevated

Table 3. Primary hyperlipidaemias.

	Lipoprotein Abnormality (WHO type)	Prevalence	Typical lipid concentrations (mmol/L) Cholesterol	Triglyceride	Risk of IHD	Pancreatitis
Common (polygenic) hypercholesterolaemia	IIa or IIb	Very common	6.5 to 9.0	< 2.3	+	–
Familial hypercholesterolaemia	IIa or IIb	Moderately common	7.5 to 16.0	< 2.3	+++	–
Familial hypertriglyceridaemia	IV or V	Common	6.5 to 12.0	10 to 30	?	++
Familial combined hyperlipidaemia	IIa, IIb, IV, or V	Common	6.5 to 10.0	2.3 to 12.0	++	–
Familial dysbetalipoproteinaemia or remnant hyperlipoproteinaemia	III	Uncommon	9.0 to 14.0	9.0 to 14.0	++	+
Abnormal lipoprotein lipase function	I	Rare	< 6.5	10.0 to 30.0	–	+++

+ = elevated risk; – = no risk; ? = uncertain risk; IHD = ischaemic heart disease

ing. After myocardial infarction cholesterol levels may be temporarily reduced for several weeks; therefore, to measure the patient's usual level of cholesterol, blood samples should be taken within a few hours of the infarction.

The majority of people with hyperlipidaemia have plasma-lipid concentrations that are only mildly or moderately elevated, and they exhibit no clinical symptoms. At the other end of the spectrum, severe hypercholesterolaemia can cause tendon, tuberous, or planar xanthomas, xanthelasma, and arcus corneae; it is also associated with an increased risk of ischaemic stroke. Severe hypertriglyceridaemia can cause acute severe abdominal pain due to pancreatitis; hepatic and splenic enlargement, eruptive xanthomas, and lipaemia retinalis may also occur. However, the main concern in patients with hyperlipidaemias is the increased risk of ischaemic heart disease. In patients with very severe hypercholesterolaemia, such as familial hypercholesterolaemia, this may occur at a very young age; in those with the heterozygous form onset of heart disease during their 20s or 30s is not unusual, and in the rarer homozygous form ischaemic heart disease may develop by the age of 10.

Treatment of hyperlipidaemias. In patients with clinical symptoms, treatment is indicated to promote the regression or non-progression of disfiguring xanthomas, or to prevent attacks of acute pancreatitis in those with severe hypertriglyceridaemia. The main aim of treatment, however, particularly in patients with only mildly elevated lipids, is to reduce the risk of ischaemic heart disease.

Since the relationship between plasma-cholesterol concentrations and ischaemic heart disease is continuous, the level at which treatment with lipid regulating drugs should be started has been widely debated. Guidelines recommend that the decision to treat should be based on the overall risk profile of the patient and that other risk factors should also be treated (see Cardiovascular Risk Reduction, p.819). Specifically, British guidelines[8] advise that, in patients with cardiovascular disease or high cardiovascular risk, drug therapy should be added to dietary therapy if total plasma cholesterol remains above 5 mmol/litre and LDL-cholesterol above 3 mmol/litre despite dietary therapy. More recent European guidelines[9] suggest a target of total plasma cholesterol below 4.5 mmol/litre and LDL-cholesterol below 2.5 mmol/litre in patients with diabetes mellitus or established cardiovascular disease; patients with total cholesterol above 8 mmol/litre or LDL-cholesterol above 6 mmol/litre require treatment irrespective of their other risk factors. US guidelines[2,6] suggest that drug treatment should be considered if the LDL-cholesterol level is 190 mg/dL or higher. For patients with 2 or more risk factors, drug therapy should be considered if the LDL-cholesterol is 160 mg/dL or higher, and for those with existing cardiovascular disease, diabetes mellitus, or particularly high risk, drug therapy should be considered if LDL-cholesterol is 130 mg/dL or higher. The US guidelines also give target LDL-cholesterol levels of less than 160 mg/dL, less than 130 mg/dL, and less than 100 mg/dL, respectively, for the three risk groups. However, based on evidence from more recent studies, it has been suggested[16] that treatment may be appropriate in some very high risk patients at LDL-cholesterol concentrations below 100 mg/dL and that a goal of below 70 mg/dL may be reasonable. Although low HDL-cholesterol is an additional risk factor, the benefits of raising HDL-cholesterol are not established and no target is therefore specified in the current guidelines.

The main methods of treating hyperlipidaemias are dietary and lifestyle changes and the use of lipid regulating drugs.[2,6,8,9] Some surgical and other procedures may also be used in familial hypercholesterolaemia (see below).

Dietary therapy should be initiated in all patients with hyperlipidaemia and is based on weight reduction in the obese and a reduction in total fat intake. UK dietary recommendations[10] include a reduction in saturated fatty acids, restriction of *trans* fatty acids, and increased consumption of long-chain n-3 polyunsaturated fatty acids; the intake of cholesterol and n-6 polyunsaturated fatty acids should also be restricted. Similar recommendations have been made in the US.[6] Increased physical exercise is also recommended. Moderation of alcohol intake is advised, particularly in patients with hypertriglyceridaemia, in whom alcohol may precipitate pancreatitis. However, more rigorous diet than that often recommended may be necessary for diet alone to be of much value,[11] and most patients will require drug therapy to achieve target lipid concentrations. Patients at low cardiovascular risk should have a trial of dietary therapy before drugs are started; but in those with established cardiovascular disease or major risk factors drug therapy and dietary changes may be started at the same time.

The principal groups of lipid regulating drugs (hypolipidaemic drugs) are the statins, fibric acid derivatives and related compounds, bile-acid binding resins, nicotinic acid and its derivatives, and the omega-3 marine triglycerides.[1,12,13] *Statins* (HMG-CoA reductase inhibitors) reduce cholesterol by stimulating an increase in LDL-receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. Their main effect is to reduce LDL-cholesterol, but they may also reduce triglycerides to a modest extent and increase HDL-cholesterol. They are generally considered to be the most effective lipid lowering drugs. *Fibrates* inhibit the synthesis of cholesterol and bile acids, and enhance the secretion of cholesterol in bile. Their main effect is to reduce triglycerides by reducing the concentration of VLDL; they also increase HDL-cholesterol and have variable effects on LDL-cholesterol. They are used mainly in patients with hypertriglyceridaemia. *Bile-acid binding resins* lower cholesterol by combining with bile acids in the gastrointestinal tract and preventing their reabsorption. This leads to an increased oxidation of cholesterol to replace the lost bile acids, and an increase in LDL-receptor synthesis on hepatocytes, resulting primarily in a reduction of LDL-cholesterol. *Nicotinic acid* inhibits production of VLDL in the liver; it lowers LDL-cholesterol and triglycerides and increases HDL-cholesterol, but adverse effects may limit its use. *Omega-3 triglycerides* primarily reduce triglycerides. *Other drugs* that may be used include cholesterol absorption inhibitors[14] such as ezetimibe; dietary supplements containing soluble fibre, such as guar gum or ispaghula, or plant stanols or sterols, may also be used to reduce cholesterol absorption. In postmenopausal women, oestrogen therapy reduces lipid concentrations, but the adverse effects may outweigh any benefit (see Effects on the Cardiovascular System, p.1538); soya protein may have a similar effect. Garlic supplements have also been promoted for hyperlipidaemia, although their effect appears to be modest.

Choice of therapy ideally depends upon the lipid profile of the individual patient since the drug groups differ in their effects on the different lipid components. In practice, most patients have common, polygenic hypercholesterolaemia, and can be treated effectively with statins as first-line therapy. Bile-acid binding resins or nicotinic acid may be alternatives, but are generally less well tolerated. Combination therapy may be required in some patients to reach target lipid concentrations, but the risk of adverse effects is increased in patients receiving statins and fibrates together (see Effects on Skeletal Muscle under Adverse Effects of Simvastatin, p.997). In patients with hypertriglyceridaemia, statins or fibrates may be used; resins should not be used alone since they may increase triglyceride concentrations.

Patients with the less common familial dyslipidaemias generally have higher lipid concentrations and require more intensive therapy. Specific treatment strategies are as follows:

- FAMILIAL HYPERCHOLESTEROLAEMIA. Patients with familial hypercholesterolaemia usually have very high plasma-cholesterol concentrations, which rarely respond adequately to diet alone and drug therapy is therefore often necessary in this high-risk group. Aggressive therapy may lead to regression of atherosclerotic lesions.[15] The first-line drugs are the statins. In severe cases combination therapy is usually required, such as a statin with a bile-acid binding resin. A low dose of the bile-acid binding resin may be sufficient. In the homozygous form of familial hypercholesterolaemia there may be a complete lack of functional LDL-receptors and drugs that act by increasing LDL-receptors, such as statins and bile-acid binding resins, may be ineffective. However, statins may be useful as adjunctive therapy in those patients who have some LDL-receptor function. In some forms of familial hypercholesterolaemia, and where plasma-cholesterol concentrations are very high, plasma-triglyceride concentrations may also be raised. In these cases a fibric acid derivative or nicotinic acid may be effective, and in more severe cases the combination of a bile-acid binding resin together with a fibric acid derivative or a statin may be used. In patients with the homozygous form liver transplantation is the most definitive treatment. Plasma exchange (weekly or fortnightly) or more selective procedures such as LDL apheresis, including the use of heparin to precipitate LDL (the HELP system—Heparin-Extracorporeal-LDL-Precipitation) may also be used in combination with lipid regulating drugs. Gene therapy is under investigation as a treatment for familial hypercholesterolaemia.
- FAMILIAL HYPERTRIGLYCERIDAEMIA. In patients with familial hypertriglyceridaemia dietary therapy is generally adequate, but drugs may be required if there is a high risk of acute pancreatitis or if there is a family history of atherosclerosis. The risk of acute pancreatitis is high when plasma-triglyceride concentrations are above 20 mmol/litre. Nicotinic acid or the fibric acid derivatives, particularly gemfibrozil, are generally recommended and may be used in combination in severe cases. Omega-3 marine triglycerides may also be of value. In severe intractable hypertriglyceridaemia, particularly type V hyperlipoproteinaemia, norethisterone has been suggested for women or oxandrolone for men.
- FAMILIAL COMBINED HYPERLIPIDAEMIA. Drug therapy may be used in patients who do not respond to dietary therapy alone. The choice will depend on the predominant lipid abnormality. A statin is the first choice in cases where hypercholesterolaemia is predominant. A fibric acid derivative may be first choice when hypertriglyceridaemia predominates, and nicotinic acid is useful where plasma concentrations of triglyceride and cholesterol are elevated to a similar degree. Bile-acid binding

resins should not be used alone since they can aggravate hypertriglyceridaemia, but they may be useful with a triglyceride-lowering drug in some patients. Treatment with a combination of drugs that lowers both cholesterol and triglyceride concentrations may be required in some patients especially in those with markedly raised plasma concentrations of triglyceride or cholesterol, as treatment of these patients with drugs effective against only the predominant lipid may produce a rise in the plasma-concentrations of the other lipid. The choice of treatment in these cases is largely empirical as responses are not always predictable in individual patients.

- FAMILIAL DYSBETALIPOPROTEINAEMIA (remnant hyperlipoproteinaemia; remnant particle disease). In this lipid disorder the degree of hyperlipidaemia is usually severe and, although it may respond remarkably to dietary therapy, drug treatment is usually necessary. Fibric acid derivatives are the first-choice drugs. Statins or nicotinic acid may also be used.
- ABNORMAL LIPOPROTEIN LIPASE FUNCTION (chylomicronaemia). No drugs currently available are useful in this disorder. The condition is treated with severe restriction of dietary fat, and the diet may be supplemented by medium chain triglycerides to improve tolerability.

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Hypertension

Hypertension, particularly essential or primary hypertension, is widespread and although usually asymptomatic, is a major risk factor for stroke and to some extent ischaemic heart disease. Control of hypertension is therefore a major aspect of cardiovascular risk reduction. National[1,2] and international[3,4] guidelines on management have been published.

Definitions. The term *blood pressure* generally means arterial blood pressure, that is the pressure of the blood on artery walls. It is usually measured indirectly in the brachial artery just above the elbow using an appropriately calibrated sphygmomanometer and is expressed in mmHg. Two measurements are made: *systolic* or maximum blood pressure (achieved during ventricular contraction of the heart) and *diastolic* or minimum blood pressure (achieved during ventricular dilatation). *Hypertension* means a higher than 'normal' blood pressure; it has been defined as the level of blood pressure above which intervention has been shown to reduce the associated cardiovascular risk. Many factors influence blood pressure, resulting in a bell-shaped distribution curve in the general population, and in consequence it is difficult to define an absolute norm. *Normal* adult blood pressure has been arbitrarily defined as a systolic pressure below 130 mmHg together with a diastolic pressure below 85 mmHg (i.e. below 130/85 mmHg), but more recent studies have suggested that optimal blood pressure, in terms of cardiovascular risk, may be lower than this. US guidelines[2] now define normal blood pressure as below 120/80 mmHg, while European[4] and British[1] guidelines classify this as optimal. Blood pressures of 130–139/85–89 mmHg are regarded as high normal[1,4] or are included in the classification of prehypertension.[2] Although hypertension was formerly defined in terms of diastolic blood pressure alone, it is now recognised that systolic pressure is also important in determining risk, and current guidelines give equal emphasis to both.

Blood pressure above 140 mmHg systolic, and/or 90 mmHg diastolic is generally considered to represent hypertension. Although classifications of mild, moderate, and severe hypertension have been widely used, these terms may be misleading since absolute cardiovascular risk is more important in determining the need for treatment and depends on other factors in addition to blood pressure. Most guidelines[1,3,4] therefore use a grading system to classify hypertension, as follows:

grade 1: 140–159/90–99 mmHg;
grade 2: 160–179/100–109 mmHg;
grade 3: ≥180/≥110 mmHg.

In the US guidelines,[2] stage 1 hypertension corresponds to grade 1, whereas stage 2 includes both grades 2 and 3.

When systolic and diastolic pressure fall into different categories the higher value is used for classification purposes. Classification and subsequent treatment decisions should be based on blood pressure measurements taken on several occasions over a period that varies according to the severity of hypertension. Ambulatory blood pressure monitoring may be used in some cases.[1,2,5] However, readings tend to be lower with ambulatory monitoring than with conventional measurement and normal and abnormal values are not yet clearly established, although recommendations have been made.[1,4,5]

In *malignant* or *accelerated hypertension* rapidly progressing severe hypertension is associated with retinopathy and often renal impairment.

Isolated systolic hypertension occurs mainly in the elderly and has been defined[1,4] as systolic pressure of 140 mmHg or more and diastolic pressure under 90 mmHg.

Origins. In the majority of cases of hypertension the cause is unknown, and such *primary* or *essential* hypertension is probably multifactorial in origin, with genotype, as well as external factors such as diet and body-weight, playing a role.[6] Hypertension may also be associated with surgery or pregnancy and is prevalent in diabetics. In a limited number of cases hypertension is *secondary* to some other condition, such as renal disease, Cushing's syndrome, phaeochromocytoma, or the adverse effects of drugs such as oestrogens, and such causes may be suspected particularly in resistant or malignant hypertension. Although treatment of the underlying condition will generally be desirable, the resultant hypertension will not necessarily be abolished by this.

Management of hypertension. Most of what follows relates to primary or essential hypertension in adults. Hypertensive crises and hypertension associated with surgery, diabetes, renal disease, or pregnancy are also discussed below under separate headings.

Hypertension may be discovered because of adverse vascular events, especially in the eyes, brain, kidneys, or heart, but is more often asymptomatic and only discovered on routine measurement of blood pressure. Once diagnosed, decisions have to be made about the need for treatment. It is well-established that hypertension is a risk factor for the development of stroke, heart failure, and renal damage, and to a lesser extent ischaemic heart disease, and a reduction in blood pressure is generally beneficial, although mortality remains higher than in non-hypertensives.[7] However, it is important to assess hypertension in the context of overall cardiovascular risk (see Cardiovascular Risk Reduction, p.819); additional considerations include the presence of target-organ disease, such as left ventricular hypertrophy or renal disease, and associated conditions such as other cardiovascular disease or diabetes. All patients with sustained hypertension of grade 2 or above can be considered at moderate to high risk and should be treated irrespective of other risk factors.[1,4] For patients with lower blood pressures, however, the decision to treat is more complex since the absolute cardiovascular risk may range from low to high depending on what other risk factors are present. Treatment of hypertension may involve both non-pharmacological and pharmacological interventions to reduce blood pressure, as well as assessment and treatment of any other cardiovascular risk factors; any co-existing diseases should also be treated. Guidelines on the management of hypertension may differ in detail, but reflect judgement on when intervention is justified.

Non-pharmacological treatment. Adopting a healthy lifestyle is beneficial for all individuals, and any patient with raised blood pressure should be encouraged to make lifestyle changes that will reduce their cardiovascular risk (see Cardiovascular Risk Reduction, p.819). Some of these changes may also reduce blood pressure,[6,8] and in those who are at low overall risk no other treatment may be needed; a trial of non-pharmacological treatment is recommended in most patients before initiating drug therapy.[1,4] Interventions that have been shown to reduce blood pressure include: reduction in excess weight; reduction in excess alcohol consumption; reduction in sodium intake; adequate exercise; reduced fat intake; and increased fruit and vegetable consumption. Other interventions that have been tried, but with less evidence of benefit, include: increased intake of potassium, magnesium, and calcium; increased polyunsaturated fat intake with reduced saturated fat intake; and relaxation therapies for stress reduction.

These lifestyle changes may also be promoted in the population as a whole, or in individuals most likely to develop hypertension, in strategies for the *primary prevention* of high blood pressure.

Pharmacological treatment. The main factors determining drug treatment relate to the blood pressure at which therapy should be initiated, the target blood pressure, and the most appropriate drug regimen to use.

When to intervene with antihypertensive drugs depend on a number of factors and guidelines take different approaches to this question. In patients with grade 1 or grade 2 hypertension, drug treatment is generally only initiated after an adequate period of observation, including blood pressure monitoring; the period depends on the level of risk but may be 3 months or longer. In the US guidelines,[2] all patients with sustained blood pressure above target levels (140/90 mmHg or 130/80 mmHg in diabetics or those with renal disease) despite lifestyle changes are recommended for drug treatment. In other guidelines,[1,4] the decision depends on both the measured blood pressure and the overall cardiovascular risk. Patients with sustained blood pressure of 180/110 mmHg or higher should receive prompt drug treatment. Those with values of 140/90 mmHg or above who are at high or very high overall risk should also receive prompt treatment.[4] If the overall risk is moderate, treatment should be initiated if the blood pressure remains at 140/90 mmHg or above after a period of monitoring; treatment may also be considered in those with lower risk.[4] The WHO/ISH guidelines[3] acknowledge that even low-risk individuals with blood pressures above 140/90 mmHg are likely to benefit from treatment, but suggests that those at higher risk should be given the highest priority. For *elderly patients* (over 60 years) the benefit of treating hypertension has been established in several trials.[9-12] Benefit is evident up to at least 80 years of age and a strict age limit to drug therapy is probably inappropriate. Guidelines therefore generally recommend that treatment decisions should not be based on age, although slower titration of drugs has been suggested[4] in older patients since they may be more susceptible to adverse effects. In the very old (those over 80 years) the benefit of initiating therapy is less clear,[13] although those already being treated should continue.[1]

Target blood pressures are controversial. There has been concern that over-aggressive reduction of diastolic pressure might increase the risk of ischaemic heart disease.[14] However, a more recent meta-analysis[15] suggested that any increased mortality at low blood pressures was not linked to antihypertensive therapy but may have been due to poor health as a cause of low blood pressure. The HOT study[16] found that effective control to maintain the diastolic pressure below 90 mmHg (at about 85 mmHg) reduced the rate of cardiovascular events, but lower pressures (of around 70 mmHg) did not provide any further benefit, while a more recent meta-analysis[17] found no evidence of a threshold for treatment benefit down to a blood pressure of at least 115/75 mmHg. Target blood pressures of below 140/90 mmHg[2,4] or below 140/85 mmHg[1] are now recommended. In diabetics the target is below 130/80 mmHg.[1-4] Similar or lower targets should also be considered in non-diabetics with nephropathy.[1,2]

The drug regimen may include drugs from a number of groups that have antihypertensive effects. These groups have differing pharmacological actions although the pre-